# Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (delta) variant. N Engl J Med. DOI: 10.1056/NEJMoa2108891

# Supplementary appendix

## Contents

## Supplementary Section S1: Secondary analysis

For the second analysis, the proportion of cases with the B.1.617.2 variant relative to the main circulating virus (the B.1.1.7 variant) was estimated by vaccination status. This analysis is restricted to samples that have been whole genome sequenced. The underlying assumption was that if the vaccine has some efficacy and is equally effective against each variant, a similar proportion of cases with either variant would be expected in unvaccinated compared to vaccinated individuals. Conversely, if the vaccine is less effective against B.1.617.2, the variant would be expected to make up a higher proportion of cases more than three weeks after vaccination, when compared to unvaccinated individuals.

This effect estimates from this analysis can be applied to VE estimates against the B.1.1.7 variant as an indirect approach for estimating VE against B.1.617.2. In this case we apply to the VE estimate against B.1.1.7 shown in Table 2 of the main paper.

### Statistical analysis

For the second analysis data on all positive samples that had been whole genome sequenced were used. The data were restricted to the period since at least 10 cases of B.1.617.2 were detected per week (week commencing 5th April 2021 onwards). The proportion of cases with B.1.617.2 relative to B.1.1.7 was calculated by vaccination status. Logistic regression was used to estimate the odds of testing positive with B.1.617.2 in vaccinated compared to unvaccinated individuals. The following covariates were included in the model irrespective of confounding: week of test and region (as a linear interaction), history of travel, ethnicity, age, sex, and clinically extremely vulnerable. Care home resident and deprivation were investigated for confounding and not included as odds ratios did not change (more than 1%). Samples were dropped from the analysis if they were repeats of the same variant within the same individual, if different variants were detected in the same individual within a 14-day period, and if the individual had received a mixed vaccination schedule (with two different vaccines) or had received two doses less than 19 days apart.

A sensitivity analysis was also undertaken comparing to the 0-13 day period post dose 1 (a period during which immune response to the vaccine would not be anticipated).(1) This was to control for possible unmeasured confounders that may be associated with both the likelihood of being vaccinated and the likelihood of being exposed to a variant. A further sensitivity analysis was conducted matching cases of B.1.617.2 to cases of B.1.1.7 on ethnicity, region, age group and week of sample, multiple matched controls per case were allowed.

### Results

Supplementary table 4 shows the adjusted odds ratios for detection of B.1.617.2 relative to B.1.1.7 in vaccinated compared to unvaccinated individuals. Odds of cases having B.1.617.2 detected in vaccinated individuals was higher than in unvaccinated individuals for dose 1 of any vaccine (OR 1.26; 95% CI 1.10-1.45) and dose 2 of any vaccine (OR 1.78; 0.87-2.97). Based on the TNCC estimates against B.1.1.7, these results would indicate effectiveness of 36% and 80% respectively for B.1.617.2. By vaccine type the reduction in vaccine effectiveness was similar for both vaccines for 1 or 2 doses: OR 1.35 (95%CI: 1.07-1.69) for BNT162b2 and OR 1.33 (95%CI: 1.15-1.53) for ChAdOx1. With BNT162b2 the odds ratio was lower after 1 dose but higher after 2 doses compared with ChAdOx1. The sensitivity analysis comparing to the 0-13 day post dose 1 period gave a similar pattern of results

though the odds ratios were generally smaller (supplementary table 5). This was also the case with the matched analysis (supplementary table 6).

## Supplementary Section S2: Further interpretation and potential limitations

### Lower 2 dose effectiveness with ChAdOx1 compared to BNT162b2

Rollout of second doses of ChAdOx1 was later than BNT162b2 and the difference may be explained by the limited follow-up after two doses of ChAdOx1 if it takes more than two weeks to reach maximum effectiveness with this vaccine. Consistent with this, 59% of those who had received 2 doses of ChAdOx1 had done so between 2 and 4 weeks prior to symptom onset compared to 33% with BNT162b2 (supplementary figure 3).

### Comparison to previously reported estimates of vaccine effectiveness against B.1.1.7 (Alpha)

Effectiveness of one dose of either vaccine against B.1.1.7 was lower than we have previously reported in the UK using similar approaches (approximately 50% compared to 60-70% previously reported).(1, 2) There are a number of possible explanations for this difference: the comparator group differs compared to earlier in the pandemic, a large proportion of adults have now been vaccinated and unvaccinated individuals may differ from those that are vaccinated, in particular among older age groups where coverage is over 90%. Most individuals now have a longer interval after their first dose compared to earlier analyses and there could be some waning in the later periods. Incidence of COVID-19 is now much lower, this means that a higher proportion of identified cases are likely to be false positives – thereby increasing misclassification, which would attenuate vaccine effects. Finally, this analysis includes a high proportion of younger adults, who are more likely to have been infected earlier on in the pandemic (before mass testing became widespread, thereby removing susceptible individuals from the unvaccinated group. Nevertheless, two dose effects were similar to those previously reported.

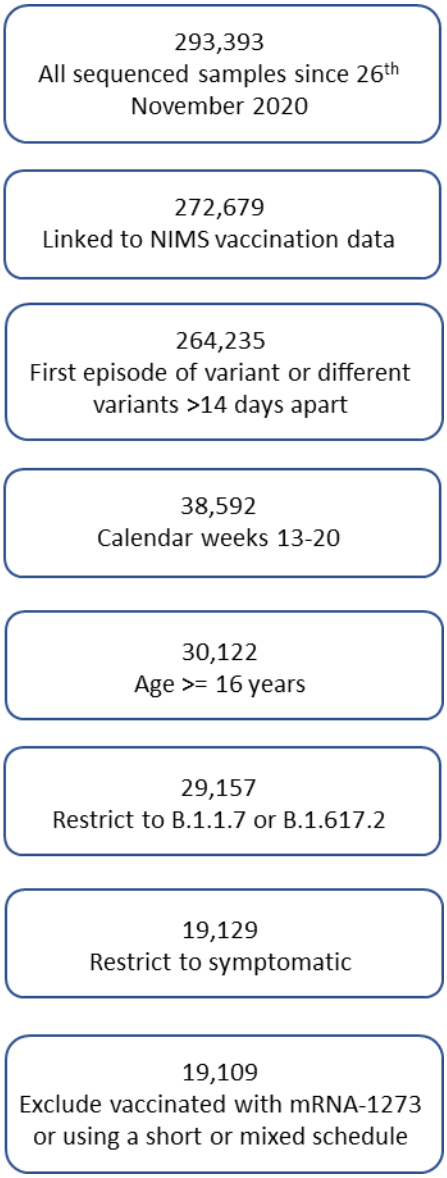


Figure S1: Exclusions and number of sequenced cases in the analysis

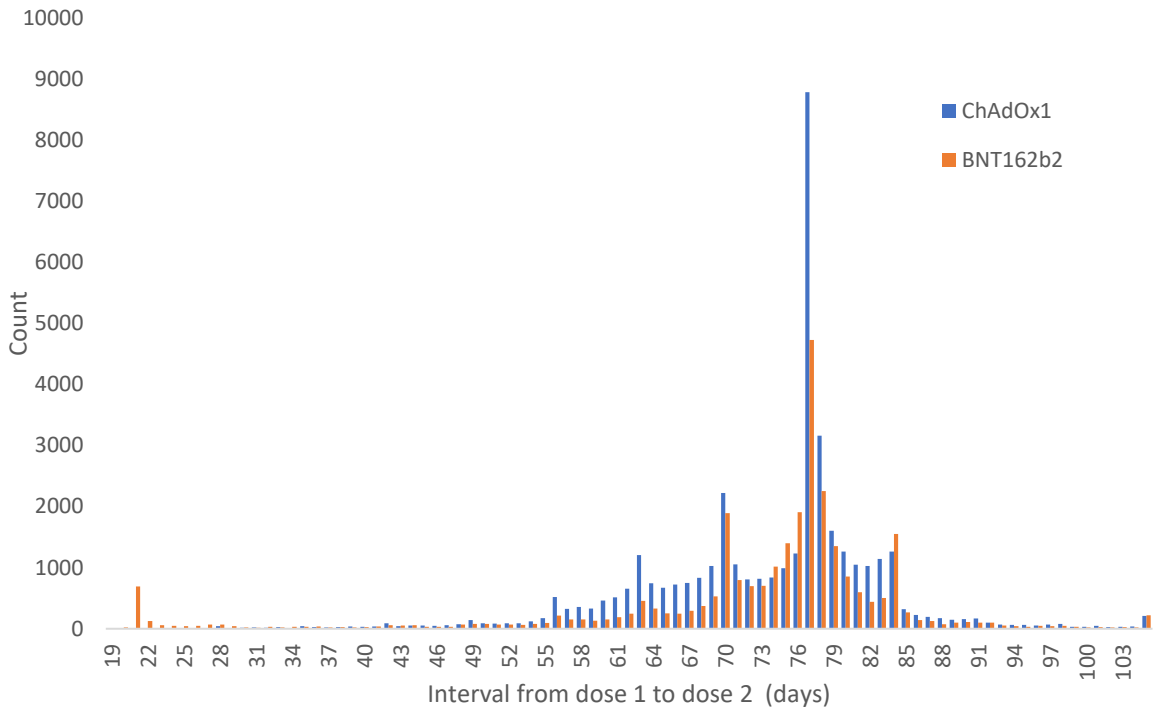


Figure S2: Interval between doses 1 and 2 by vaccine for all cases and controls receiving 2 doses in the TNCC analysis

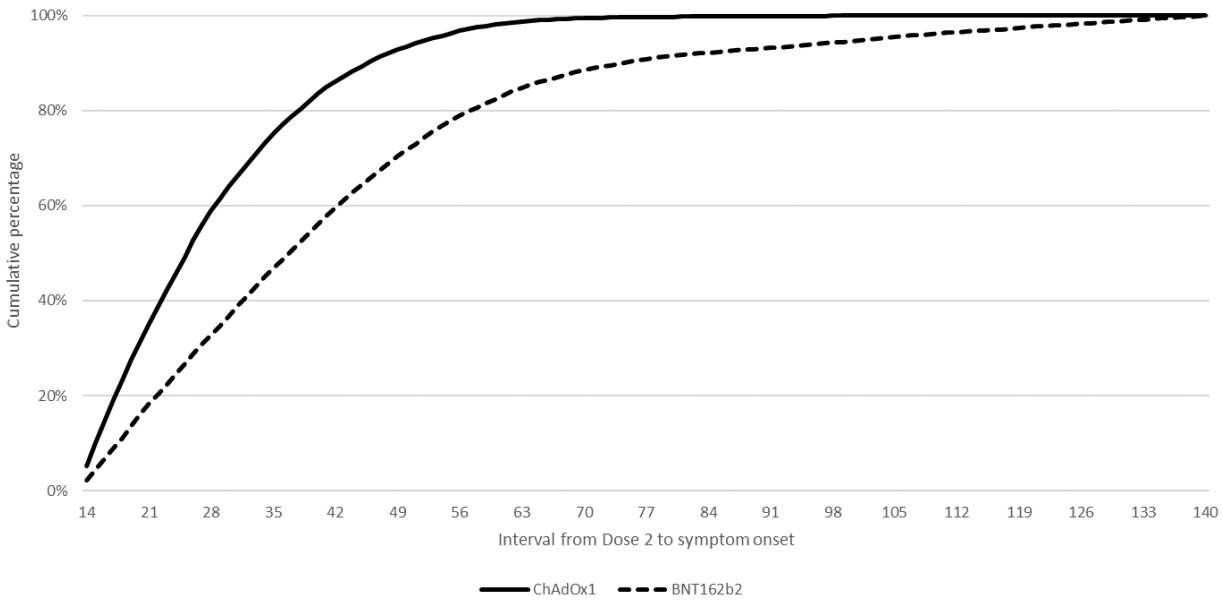


Figure S3: Cumulative proportion of those with 2 doses more than 14 days after dose 2 vaccinated by each time point after the second dose

## Table S1: Cross-tabulation of S-gene target status and variant as identified by whole genome sequencing

| Variant | S-gene | | | Total |
|---|---|---|---|---|
| | positive | negative | unknown | |
| No sequencing result | 3215 | 2,170 | 755 | 6,140 |
| B.1.1.7 | 2 | 7,991 | 381 | 8,374 |
| B.1.1351 | 32 | 0 | 4 | 36 |
| B.1.617.2 | 3460 | 2 | 110 | 3,572 |
| P.2 | 15 | 0 | 2 | 17 |
| B.1.617.1 | 42 | 0 | 10 | 52 |
| B.1.617.3 | 3 | 0 | 0 | 3 |
| B.1.525 | 0 | 20 | 0 | 20 |
| B.1.1.318 | 18 | 0 | 1 | 19 |
| AV.1 | 16 | 0 | 3 | 19 |
| C.36.3 | 0 | 6 | 1 | 7 |
| Low quality (likely B.1.617.2) | 14 | 0 | 3 | 17 |
| Not VOC/VUI | 30 | 1 | 0 | 31 |
| Total | 6,847 | 10,190 | 1,270 | 18,307 |

## Table S2: Cross-tabulation of S-gene target status and variant as identified by whole genome sequencing after dropping non B.1.1.7 or B.1.617.2 variants and reassignment based on sequencing results

| Variant | S-gene | | | Total |
|---|---|---|---|---|
| | positive | negative | unknown | |
| No sequencing result | 3215 | 2,170 | 755 | 6,140 |
| B.1.1.7 | 0 | 8,374 | 0 | 8,374 |
| B.1.617.2 | 3572 | 0 | 0 | 3572 |
| Total | 6,787 | 10,544 | 755 | 18,086 |

## Table S3: Vaccine effectiveness against S-gene target negative (B.1.1.7) and S-gene target positive (B.1.617.2) – stratification by interval post dose 1

| Vaccination status | Test negative controls | B.1.1.7 or S-gene target negative | | | B.1.617.2 or S-gene target positive | | |
|---|---|---|---|---|---|---|---|
| | | cases | cases:controls | aVE(%) | cases | cases:controls | aVE(%) |
| Unvaccinated | 96371 | 7313 | 0.076 | base | 4043 | 0.042 | base |
| | | | | | | | |
| BNT162b2 | | | | | | | |
| Dose 1 (21-55 days) | 2884 | 144 | 0.050 | 56.9 (48.6 to 63.8) | 43 | 0.015 | 32.7 (7 to 51.3) |
| Dose 1 (56+ days) | 5757 | 306 | 0.053 | 41.3 (33.4 to 48.2) | 94 | 0.016 | 36.7 (21.3 to 49.1) |
| Dose 2 | 15749 | 49 | 0.003 | 93.7 (91.6 to 95.3) | 122 | 0.008 | 88.0 (85.3 to 90.1) |
| | | | | | | | |
| ChAdOx1 | | | | | | | |
| Dose 1 (21-55 days) | 25913 | 1207 | 0.047 | 49.7 (45.9 to 53.2) | 592 | 0.023 | 34.6 (27.7 to 40.8) |
| Dose 1 (56+ days) | 16916 | 569 | 0.034 | 45.9 (40.4 to 51) | 764 | 0.045 | 25.5 (18 to 32.3) |
| Dose 2 | 8244 | 94 | 0.011 | 74.5 (68.4 to 79.4) | 218 | 0.026 | 67.0 (61.3 to 71.8) |

aVE= adjusted vaccine effectiveness, adjusted for period (calendar week), travel history, ethnicity, sex, age, IMD, CEV, region, previous history of positive test, health/social care worker, care home resident

## Table S4: Odds ratios for detection of B.1.617.2 relative to B.1.1.7 in vaccinated compared to unvaccinated individuals

| Vaccination status | Number of cases | | Ratio B.1.617.2 to B.1.1.7 | OR | aOR |
|---|---|---|---|---|---|
| | B.1.1.7 | B.1.617.2 | | | |
| Unvaccinated | 10509 | 2708 | 0.258 | base | base |
| Any vaccine | | | | | |
| Dose 1 | 2866 | 950 | 0.331 | 1.25 (1.13-1.39) | 1.26 (1.10-1.45) |
| Dose 2 | 162 | 167 | 1.031 | 1.87 (1.45-2.41) | 1.78 (1.29-2.45) |
| Dose 1 or 2 | 3294 | 1262 | 0.383 | 1.33 (1.22-1.46) | 1.33 (1.17-1.53) |
| BNT162b2 | | | | | |
| Dose 1 | 670 | 113 | 0.17 | 1.2 (0.95-1.53) | 1.17 (0.88-1.54) |
| Dose 2 | 57 | 71 | 1.25 | 2.65 (1.75-4) | 2.42 (1.47-3.98) |
| Dose 1 or 2 | 845 | 228 | 0.270 | 1.45 (1.20-1.74) | 1.35 (1.07-1.69) |
| ChAdOx1 | | | | | |
| Dose 1 | 2196 | 837 | 0.381 | 1.26 (1.13-1.41) | 1.28 (1.1-1.49) |
| Dose 2 | 105 | 96 | 0.914 | 1.52 (1.1-2.08) | 1.47 (0.99-2.18) |
| Dose 1 or 2 | 2449 | 1034 | 0.422 | 1.31 (1.18-1.45) | 1.33 (1.15-1.53) |

aOR = Adjusted odds ratio – adjusted for: week of test and region (as linear interaction), history of travel, ethnicity, age, sex, clinically extremely vulnerable, care home resident

## Table S5: Odds ratios for detection of B.1.617.2 relative to B.1.1.7 in vaccinated individuals compared to the <14 days post dose 1

| Vaccination status | Number of cases | | Ratio B.1.617.2 to B.1.1.7 | aOR |
|---|---|---|---|---|
| | B.1.1.7 | B.1.617.2 | | |
| Days 0-13 post dose 1 | 10509 | 2708 | 0.258 | base |
| | | | | |
| Any vaccine | | | | |
| Dose 1 | 2866 | 950 | 0.331 | 1.15 (0.89-1.48) |
| Dose 2 | 162 | 167 | 1.031 | 1.62 (1.10-2.37) |
| Dose 1 or 2 | 3294 | 1262 | 0.383 | 1.21 (0.94-1.56) |
| | | | | |
| Any vaccine | | | | |
| Dose 1 | 670 | 113 | 0.17 | 1.06 (0.74-1.5) |
| Dose 2 | 57 | 71 | 1.25 | 2.2 (1.28-3.77) |
| Dose 1 or 2 | 845 | 228 | 0.270 | 1.22 (0.89-1.67) |
| | | | | |
| Any vaccine | | | | |
| Dose 1 | 2196 | 837 | 0.381 | 1.16 (0.9-1.5) |
| Dose 2 | 105 | 96 | 0.914 | 1.34 (0.85-2.09) |
| Dose 1 or 2 | 2449 | 1034 | 0.422 | 1.21 (0.94-1.56) |

aOR = Adjusted odds ratio – adjusted for: week of test and region (as linear interaction), history of travel, ethnicity, age, sex, clinically extremely vulnerable, care home resident

## Table S6: Matched case control analysis

| Vaccination status | Number of cases | | Ratio B.1.617.2 to B.1.1.7 | aOR compared to unvaccinated | aOR compared to <14 days post dose 1 |
|---|---|---|---|---|---|
| | B.1.1.7 | B.1.617.2 | | | |
| Unvaccinated | 4902 | 1644 | 0.335 | base | |
| <14 days post dose 1 | 264 | 118 | 0.447 | | base |
| | | | | | |
| Any vaccine | | | | | |
| Dose 1 | 1159 | 476 | 0.411 | 1.13 (0.96-1.32) | 0.99 (0.74-1.32) |
| Dose 2 | 90 | 74 | 0.822 | 1.97 (1.36-2.85) | 1.74 (1.12-2.69) |
| Dose 1 or 2 | 1366 | 616 | 0.451 | 1.21 (1.04-1.40) | 1.06 (0.80-1.41) |

Matched on Ethnicity, Region, age(10 yrs), week of sample

## References

1. Lopez Bernal J, Andrews N, Gower C, Robertson C, Stowe J, Tessier E, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ. 2021;373:n1088.

2. Public Health England. Public Health England vaccine effectiveness report - March 2021: Public Health England; 2021 [Available from: https://www.gov.uk/government/publications/phe-monitoring-of-the-effectiveness-of-covid-19-vaccination.